

Suspected Post-Chemotherapy Cardiomyopathy Hiding Severe Three-Vessel Coronary Artery Disease in a Young Patient with Metabolic Syndrome: Should an Early Angiography be Recommended?

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Abstract- Cardiotoxicity is one of the most important adverse event related to anthracycline therapy and can lead in about 1-5% of cases to the occurrence of heart failure. In a higher percentage of patients treated with these drugs asymptomatic left ventricular dysfunction can occur, so that guidelines recommend a strict clinical and echocardiographic monitoring. However, the occurrence of left ventricular dysfunction can be multifactorial and the search of other concurrent etiologies, including ischemic heart disease, is pivotal in particular in patients at high cardiovascular risk. Here is reported the case of a young man with metabolic syndrome in whom the presence of ischemic heart disease was suspected six years after the diagnosis of cardiomyopathy following treatment with anthracyclines for an Hodgkin's lymphoma; in fact, he was submitted to angiography only when symptoms of angina occurred in addition to left ventricular dysfunction. In this patient coronary angiography showed severe coronary artery disease which was treated with angioplasty and stenting. The present case suggest that also in young patients treated with anthracyclines developing left ventricular dysfunction, ischemic heart disease should be suspected in particular for those at high cardiovascular risk. To exclude this diagnosis a cardiac stress test or coronary angiography/computed tomography should be recommended.

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Introduction

Anthracycline medications are effective for the treatment of many malignancies but their use is limited by their possible cardiotoxicity as well as other hematological, gastroenteric and cutaneous disorders, so that guidelines for the monitoring of adverse effects should be strictly followed (1).

Cardiac events may include mild blood pressure changes, thrombosis, electrocardiographic changes, arrhythmias, myocarditis, pericarditis, myocardial infarction and cardiomyopathy with left ventricular dysfunction leading to congestive heart failure. This latter is the most important clinical consequence and can occur in about 1-5% of cases; asymptomatic decrease in left ventricular dysfunction can be found in about 5-20% of cases (2). The pathophysiologic mechanism of this disease can be ascribed to myocytes death induced by these drugs, through oxidative stress and

apoptosis.

However, present guidelines for the monitoring of chemotherapeutic adverse events do not furnish clear indications with regard to the diagnostic evaluations of patients presenting with left ventricular dysfunction after treatment with anthracyclines in particular in relation to their age and individual cardiovascular risk profile.

Case Report

A 42 years-old man with metabolic syndrome (MetS) (3) was admitted to our cardiac Step Down Unit for stable angina. Six years before he was treated with chemotherapy including high dose anthracyclines for a Hodgkin's lymphoma (stage 4, Ann Arbor). After chemotherapy the patient was submitted to an echocardiogram showing a moderate left ventricular dysfunction which was, at that time, primarily ascribed

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Post-chemotherapy cardiomyopathy

to anthracyclines administration (1,4) despite a high cardiovascular risk profile for severe dyslipidemia, hypertension, obesity and smoking (5,6). In the subsequent years the patient felt asymptomatic, examinations at follow-up showed complete remission of neoplastic disease and no variation in echocardiographic findings. Five years after chemotherapy administration the patient was admitted to hospital for acute heart failure. During hospitalization echocardiography showed diffused hypokinesia with moderate left ventricular dysfunction (ejection fraction 40%), which was ascribed to the progression of toxic hypokinetic cardiomyopathy. Few months later the patient complained with angina for moderate exertion, so after cardiologic evaluation he was admitted to our unit to perform coronary angiography.

Echocardiography confirmed moderate left ventricular dysfunction. Blood examinations revealed a type IIb of dyslipidemia (total cholesterol 444 mg/dl, HDL cholesterol 22 mmg/dl, triglycerides 2655 mg/dl), impaired fasting glycemia (HbA1c 6.5%), hyperuricemia (7.2 mg/dl) and mild renal dysfunction. Blood pressure control during continuous monitoring showed moderate hypertension.

At coronary angiography severe three-vessel disease was detected, with occlusion in the middle part of the right coronary artery, stenosis of 50% of left anterior descending in the first part followed by critical stenosis in the middle part, involving the origin of the second diagonal branch and subocclusive stenosis of circumflex artery in the first part. Despite a high Syntax Score (7), considering also the patient young age, percutaneous myocardial revascularization was chosen with coronary angioplasty and drug eluting stent implantation on left anterior descending and circumflex arteries. After revascularization it was not possible to assess the efficacy of dual anti-platelet therapy by means of platelet aggregation tests because of lipemic sample. Considering the sites of stent implantation and the high thrombotic risk, clopidogrel 75 mg was replaced by prasugrel 10 mg associated with aspirin 100 mg. A therapy with beta-blocker and ACE-inhibitor was also started. For lipid profile control we acquired a dietetic consult, and a low lipid diet was planned in association with high dose of statins and fibrates. After four days of hospitalization the patient was discharged. The patient was completely asymptomatic, lipid-lowering therapy was effective in reducing total cholesterol and triglycerides (362 mg/dl and 1488 mg/dl, respectively).

Discussion

Cardiac dysfunction is a well known adverse event related to anthracyclines treatment. However, when this complication occurs other possible causes of left ventricular dysfunction should be ruled out, in particular the contemporary presence of coronary artery disease in patients at high cardiovascular risk.

Here we report the case of a young man with MetS and left ventricular dysfunction after chemotherapy with anthracyclines for an Hodgkin's lymphoma. Cardiac dysfunction was initially ascribed to these drugs, and no other diagnostic evaluations were performed to exclude the concomitant presence of an underlying ischemic heart disease. Current guidelines for the follow-up of patients treated with anthracyclines provide the need of continuous baseline cardiac function monitoring during therapy, with regular electrocardiographic and echocardiographic studies, radionuclide angiography, an optimal follow-up cardiac evaluation schedule, measurement of serum electrolytes and cardiac enzymes and the addition of risk stratification to monitoring schemes (8).

However, no mention to the possible exclusion of a coronary artery disease after the occurrence of post-chemotherapy left ventricular dysfunction is reported in these guidelines, either in relation to each patient age or individual cardiovascular risk. In our patient no direct or indirect assessment for the search of ischemic disease was performed even in the presence of multiple cardiac risk factors most of which leading to the diagnosis of MetS. Coronary angiography has been only proposed after the occurrence of angina and showed a severe three-vessel coronary artery disease.

We suppose that an early diagnosis and treatment of this disease should have been safer for this patient and should have helped in preventing cardiac damage and atherosclerotic disease. Further studies should be performed to furnish in future guidelines possible indications on the execution of a cardiac stress test or a coronary angiography for patients developing left ventricular dysfunction after anthracyclines administration, considering also patient age and individual cardiovascular risk profile.

In our belief, coronary angiography or, at least, cardiac computed tomography in selected cases, should be mandatory to rule out an underlying coronary artery disease in patients with left ventricular dysfunction after chemotherapy treatment, in particular in the presence of a high cardiovascular risk (probability of cardiac events superior to 50% in ten years). In fact, the exclusion of

coronary artery disease is a first line assessment to detect the correct etiopathogenesis of cardiac dysfunction and its treatment. Our patient cardiac risk profile pattern was clearly classifiable as MetS, a constellation of obesity, hypertension, dyslipidemia, hyperuricemia and insulin resistance, that is increasing in prevalence in the American population and also worldwide (9). Patients with MetS are at risk of developing atherosclerosis and have an increased cardiovascular and all-cause mortality. In these patients, in order to prevent acute cardiac events, a continuous cardiac monitoring is advised either with baseline electrocardiography and echocardiography and with a provocative stress testing.

Current treatment strategies for these patients include lifestyle modifications and a specific pharmacological approach. Weight loss, blood pressure control, cholesterol levels reduction and treatment of hyperglycemia are advised. In fact, several studies have shown improvement in left ventricular function and decreased mortality and morbidity from heart failure after the adoption of these strategies.

Another important issue is the optimal anti-platelet strategy that should be administered to these patients. In fact, after stent implantation, the persistence of severe dyslipidemia led us to start therapy with prasugrel since we could not be able to assess platelet response to anti-platelets. This strategy was chosen also given the high thrombotic risk of patients with MetS, mainly driven by a reduced thrombolytic activity (10) and an increased platelet aggregation (11). However, no data are available in literature regarding the optimal anti-platelet therapy of patients with MetS and severe dyslipidemia except for the subgroup of those presenting also with diabetes mellitus (12). In our belief, these patients should be treated with third generation more potent thienopyridines unless otherwise contraindicated.

In conclusion, post-chemotherapy left ventricular dysfunction can often hide severe ischemic heart disease, in particular in patients with MetS or at high cardiovascular risk.

We believe that in patients at high cardiovascular risk, older than 35 years, developing left ventricular dysfunction after anthracyclines administration, coronary angiography/computed tomography or, at least, a cardiac stress test should be recommended.

Finally, a peculiar attention should be given to the optimal anti-platelet therapy when stent implantation is necessary preferring third generation thienopyridines above all when severe dyslipidemia cannot allow to correctly assess the response to anti-platelet therapy.

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